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A systematic review and meta-analysis of the role of sugar-free chewing gum in dental caries

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Abstract:	Aim: To determine the difference in level of dental caries in adults and children who chew sugar-free gum (SFG), compared with those who do not chew SFG or use alternatives such as lozenges, candies, rinses, tablets and other non-chewing controls. Methods: Systematic review of published literature. Results: Twelve studies of interventions of SFG for dental caries outcomes were included. SFGs were found to significantly reduce caries increment, giving a Preventative Fraction (PF) of 28% (95%CI 7% to 48%). Including the eight trials that used xylitol gum only as the basis of the intervention, the PF was 33% (95% CI 4% to 61%). No adverse effects were recorded. There was a high level of heterogeneity among the trials included. Conclusion: The findings of this review provide tentative evidence that chewing sugar-free gum reduces caries increment in comparison to non-chewing controls. However, there is a considerable degree of variability in the effect and the trials included were generally of moderate quality. There is a need for future research to explore the acceptability and feasibility of the use of SFG as a public health intervention.

A systematic review and meta-analysis of the role of sugar-free chewing gum in dental caries

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Knowledge Transfer Statement: The results of this study can be used by clinicians when deciding how best to implement dental caries prevention regimes for their patients. With consideration of cost and patient preference, this information could help to develop national policy directives on caries prevention and dictate the direction of future clinical research.

Abstract

Aim: To determine the difference in level of dental caries in adults and children who chew sugar-free gum (SFG), compared with those who do not chew SFG or use alternatives such as lozenges, candies, rinses, tablets and other non-chewing controls.

Methods: Systematic review of published literature.

Results: Twelve studies of interventions of SFG for dental caries outcomes were included. SFGs were found to significantly reduce caries increment, giving a Preventative Fraction (PF) of 28% (95%CI 7% to 48%). Including the eight trials that used xylitol gum only as the basis of the intervention, the PF was 33% (95% CI 4% to 61%). No adverse effects were recorded. There was a high level of heterogeneity among the trials included.

Conclusion: The findings of this review provide tentative evidence that chewing sugar-free gum reduces caries increment in comparison to non-chewing controls. However, there is a considerable degree of variability in the effect and the trials included were generally of moderate quality. There is a need for future research to explore the acceptability and feasibility of the use of SFG as a public health intervention.

Introduction

Despite improvements in oral health, the burden of oral disease remains high in both developing and developed countries. Chewing sugar-free gum (SFG) is emerging as a possible adjunct to existing prevention strategies [Wessel et al 2016], through mechanisms such as its stimulation of saliva, mechanical plaque control as well as acting as a carrier for bacteriostatic ingredients including xylitol and sorbitol [Van Loveren 2004]. The oral care benefits of chewing SFG are recognised and supported by regulatory bodies such as the European Commission [European Commission 2012a, European Commission 2012b] and the European Food Safety Authority [EFSA Panel on Dietetic Products, Nutrition and Allergies 2010], as well as the FDI World Dental Federation [FDI World Dental Federation. 2015], the United Kingdom (UK) Oral Health Foundation [Oral Health Foundation 2018] and numerous other national dental associations worldwide.

A number of prospective clinical studies of caries incidence and SFG use have been conducted over the past 40+ years (Moller et al 1973, Glass 1983, Isokangas et al 1988, Kandelman and Gagnon 1990, Mäkinen et al 1995, Mäkinen et al 1996, Beiswanger et al 1998, Kovari et al 2003, Tao et al 2013), together with reviews of the available literature at the time. Some include SFG as part of a broader review of preventive products (Riley et al 2015, Rethman et al 2011). Others rely on expert opinion (Ly et al 2008, Burt 2006). There are two systematic reviews (Mickenautsch et al 2007, Deshpande and Jadad 2008), both of which are over 10 years old. Recent research publications on the economic benefits of increased consumption of sugar-free gum in the UK and globally (Claxton and Kay 2016, Rychlik et al 2017), have provided an opportunity to quantify the oral care benefits of chewing SFG, develop further research initiatives and, in so doing, re-engage policy makers and regulatory agencies to consider the inclusion of chewing SFG, alongside established behaviours, in guidelines to support improved oral health. However, the broad applicability of the findings of the economic evaluations has been questioned. For example, the UK health economic study based its data modelling on results from a single study published in 2001 conducted in Lithuania (Machiulskiene 2001). Similarly, the global economic model was based on results from four studies, published between 2000 and 2004, conducted in Lithuania, Hungary, Estonia and China (Machiulskiene et al 2001, Peng et al 2004, Alanen et al 2000, Szoke et al 2001).

Therefore, there is a definite need to update and refresh the existing knowledge base in relation to SFG both in relation to dental caries but also its effect on the broader aspects of oral health. This paper will describe the findings of a systematic review of studies exploring the relationship between use of SFG and dental caries, as part of a larger review of the role of sugar-free gum in oral health. The research question addressed in this manuscript is "What is the difference in level of dental caries in adults and children who chew SFG, compared with those who do not chew SFG or use alternatives such as lozenges, candies, rinses, tablets and other non-chewing controls?"

Methods

Protocol and registration

The methodology for this systematic review was registered on PROSPERO 2018 (CRD42018094676).

Eligibility Criteria

Manuscripts reporting studies meeting the following criteria were included:

- Human participants: adults and children
- Primary research, published from 1 January 1946 to 30 September 2018
- Study designs: trials including Randomised Controlled Trials (RCTs), crossover trials, pre-post trials, pre-post one arm trials, post-only trials and any design with a comparative arm. Crossover trials were required to have a minimum 'washout period' of one week between intervention arms.
- English Language. The researchers were unable to access translation facilities for non-English studies.

Manuscripts reporting the following were excluded:

- Reports of reviews - systematic or narrative reviews
- Non-experimental studies
- Laboratory-based studies
- Follow-up studies of previous trials where the original intervention / control allocation had been changed on any basis, for example self-reported behaviour, assessed level of use of active intervention.
- Conference abstracts that did not give rise to subsequent full publication

Interventions:

Studies that had the chewing of SFG as the main intervention were included. “Sugar” in this review refers to monosaccharides (i.e. glucose, fructose, galactose) and disaccharides (i.e. sucrose, lactose, maltose). It does not include polyols such as xylitol, sorbitol or malitol; therefore, the use of these polyols in gums satisfied “sugar-free” criteria.

Outcomes:

Outcomes relating to an agreed list of multiple oral health related outcomes were examined. For the purposes of this manuscript the following outcomes relating to dental caries were included:

- DMFT/DMFS increment
- dmft/dmfs increment

In addition, data were collected on adverse consequences (negative effects and harm) of SFG that were reported within the included studies, alongside acceptability and implementation methods that have been shown to lead to greater adherence.

Information Sources and Search

The search strategy was designed and undertaken by an information specialist (SDG). Search terms were based on both Medical Subject Headings (MESH), and free text with combinations of chewing gum, sugar free, caries, xerostomia, periodontal disease (see Figure 1). Once fully developed by searching one database (OVID Medline), the detailed search was then adapted for all the relevant databases with appropriate modifications: Ovid MEDLINE, Ovid EMBASE, Ovid PsycINFO, Scopus, Web of Science, Allied and Complimentary Medicine Database (AMED), Cochrane Central Register of Controlled Trials (CENTRAL), Open Grey, as well as searching Prospero and the Cochrane library of systematic reviews. Reference lists of included studies and any relevant systematic reviews identified were also searched.

Study selection

Initial screening of articles identified in the database searches involved independent screening of titles and abstracts by two reviewers (OA / AB), on the basis of the research question (PICO specification) and against the inclusion and exclusion criteria. Following this

assessment, the full text of all potentially relevant studies was checked for eligibility. Disagreements between reviewers was resolved by the input of a third reviewer (JTN). Study authors were contacted where further clarification was required to determine eligibility or to ascertain methodological details. All references from identified papers were also reviewed to see if any additional papers could be identified meeting the initial inclusion criteria and seven additional papers were included (JTN/MN).

After data extraction, additional articles were excluded because: the direct effect of SFG was not the primary focus of intervention; trial design (having a washout period of less than 7 days); outcomes were not relevant; they did not involve SFG, or SFG alone or it was unclear if they actually included SFGs; reviews/commentaries which did not represent trials/experimental studies; participants not analysed in their original allocated groups; full text not available in English (a total of 15 papers were excluded because they were not available in English. Only six of the manuscripts excluded for this reason related to caries outcome, the remaining nine assessed plaque and salivary changes).

Meta-analysis was undertaken using data recorded at baseline and at the end of the study, regardless of when this was. Where there were multiple papers reporting outcomes at successive time points, only the final time point published was included. Where more than one SFG was used, the results were combined and this was compared to the control group [29] and separate analysis was also undertaken comparing xylitol SFG to a control group. Separate analysis of xylitol-only gums was included since this appeared to be the most frequently adopted SFG in trials and the investigators wished to determine whether any recommendations could be made for xylitol gum specifically. Where the data for either the control or SFG group was available at both baseline and at the end of the study, the paired data were re-created using the method outlined by Borenstein et al 2011. The correlation between the baseline and the end of study data was assumed to be 0.95 for the control and 0.65 for the SFG group. A sensitivity analysis was conducted with the correlation set at 0.95 for the SFG group.

Data collection process

Data were extracted from each included study based on the pre-determined list of outcomes of interest. This was undertaken in duplicate by three reviewers (OA, MN and

JTN) who also developed and piloted the data extraction form prior to extraction. Two reviewers extracted the data from all studies, calling on the third reviewer in the case of disagreement. A total of 29 study authors were contacted: no response was received from 14, and a further 7 responded but were unable to provide the information requested asked.

Data items

Data on caries were recorded as above. In addition, for each included study, data were extracted on the potential effect modifiers such as:

- The intervention: *who delivered it, the setting, details of gum used e.g. ingredients and concentrations, recommended usage e.g. frequency of use, duration of use,*
- Participant characteristics: *age, social class, sample size, diet, pre-existing conditions, risk of population, oral hygiene details*
- Relevant study details: *number of participants in each arm at baseline and included in analysis, number of withdrawals, follow up period, washout period, unit of randomisation, unit of analysis*
- Bibliographic details: author(s), title, journal, country of origin, year of publication, trial design.

Differences were resolved through discussion and the input of a fourth reviewer if necessary (AB). Study authors were also contacted if there were missing data. Where the same study was reported across several different publications, data were extracted just once but all publications were used to ensure data extraction was maximised across all dimensions under investigation.

Risk of bias in individual studies

Using the Cochrane tool for assessing risk of bias (Higgins et al 2011), three reviewers (OA, JTN, MN) assessed all included studies independently across six domains: selection, performance, detection, attrition, reporting and 'other' biases. The option for disagreements to be resolved through discussion and with the input of a fourth reviewer (AB) as required was available.

Summary measures

Three summary measures were calculated: the prevented fraction (PF), standardised mean difference (SMD) and standardised effect size (ES). The effect size was calculated using the procedure metaeff in Stata v15.1 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). The metaan command in Stata v15.1 was then used to conduct a random effects maximum likelihood meta-analysis and draw forest plots.

Risk of bias across studies

Whenever concerns were encountered regarding incomplete data, data in graphs or figures, pooled data, incomplete information on key elements of the data extraction form, an attempt was made to contact the authors for clarification. If authors could not be contacted the paper was excluded. If authors responded with clarification or missing data, this information would be communicated to the statistician for validity. If valid, the papers were included and data extraction sheets were completed.

Changes to protocol following commencement of study

Following the commencement of the study the decision was made to exclude studies with incomplete outcome data unless contact with the authors could ensure that the data was complete. For the caries outcome data no study was excluded due to incomplete data. Sensitivity analyses had been planned based on the characteristics of the participants and the risk of bias. However there was little variation across the studies in these variables, so no sensitivity analyses were conducted. In the protocol, the analytical strategy stated that analyses would include all covariates (effect modifiers), but these were not included in the analyses reported here.

Results

The search strategy identified 38 manuscripts which explored the impact of chewing SFG on oral health outcomes, across all aspects of oral health. Of these, a total of 17 full text articles, reporting the findings of 12 studies with dental caries outcomes were included in this systematic review – all of which were included in the overall meta-analysis. Of these, eight studies had used xylitol gum as the basis of the intervention and so were included in a separate meta-analysis. Figure 2 shows the PRISMA flow chart for identification of manuscripts included in this review. Table 1 summarises the characteristics of the studies

included in the review, including the mean caries increments in each study arm within the individual studies.

The analysis of the risk of bias within individual studies included in the review is summarised in Table 2. Of the 12 studies included in the review, 11 (91.7%) were randomised controlled trials (RCTs) and one (8.3%) was a pre-post study. The randomisation of participants was clear for the RCTs but there was a risk of bias in group allocation for the crossover trials. For seven of the trials there was a high risk that participants were aware of the arm of the trial to which they had been allocated with the potential for bias that entails. For all trials except one, it was unclear whether the reported results included all outcomes or whether particular outcomes had been selected to report with the possibility that there was a bias towards the reporting of positive findings.

The results of the meta-analysis are represented in Figure 3. In order to account for the variations in outcomes and the reporting of the caries increment data including the ranges of the control and test SFG arms between the studies, the preventive fraction (PF) was calculated to produce a more clinically meaningful outcome measure. The use of SFG significantly reduced caries increment (PF 28%; 95% CI 7% to 48%; SMD 0.32 95% CI 0.09 to 0.54; ES -0.33; 95% CI -0.62 to -0.05). There was a high degree of variability amongst the estimates and a high level of heterogeneity between studies with I^2=94.7%. Changing the correlation between the baseline and end of study data to 0.95 for the SFG gave similar results (PF 30%; 95% CI 8% to 51%; SMD 0.35 95% CI 0.12 to 0.58; ES -0.39; 95% CI -0.73 to -0.06). In six of the 12 studies the confidence intervals of the effect size estimate included zero, suggesting no effect of the intervention.

A separate meta-analysis of trials where the intervention comprised xylitol gum only was undertaken. Xylitol gum reduced caries increment but again, there was a wide variability in the estimates of effect (PF 33%; 95% CI 4% to 61%; SMD 0.39; 95% CI -0.01 to 0.79; ES -0.40; 95% CI -0.81 to 0.02). There was a high level of heterogeneity between studies with I^2=91.5%.

No adverse events were reported in any of the studies.

Discussion

This systematic review and meta-analysis confirms the effect of SFG in reducing dental caries and the potential for SFG to be considered an adjunct to preventive oral health care regimes. The overall effect size for all sugar-free gums (-0.30) compares favourably to other preventive interventions, such as oral health education (Stein et al 2018) and supervised toothbrushing programmes (Dos Santos et al 2018), perhaps because the chewing of gum not only increases saliva flow but also acts as a behaviour incompatible with other caries risk behaviours such over consumption of sugar-containing foods. A strength of the studies reviewed is the duration of follow up, which ranged from 7 weeks to 6 years with approximately two-thirds of studies having follow up period of two or more years. Given the current knowledge of the natural history of the caries process, it is critical that any future studies incorporate a duration of follow up that is sufficient to reflect the outcomes of the caries process.

There was a high level of heterogeneity in the trials both in terms of the dosage and frequency of use of the SFGs, as well as in the length of follow-up. Further research is required to determine the optimum balance between efficacy and acceptability to the population targeted. It is likely that the perceptions of acceptability of the use of SFG will vary across age and other socio-cultural characteristics of the targeted population. The availability of SFG in society has never been higher (Neiburg 2012). There is also the possibility of additional health benefits - evidence from a recent Cochrane review suggests that for healthy children and children with respiratory infections, chewing xylitol gum helps prevent acute otitis media in children up to 12 years old (Hanno et al 2011). In addition, data on the cost-effectiveness of SFG as an intervention is supportive (Claxton and Kay 2016, Rychlik et al 2017). The majority of trials in this study recruited children as participants, with only one trial having adult participants and one recruiting mother-child dyads. Caution should be exercised in generalising the findings beyond children and young people, however. There is a need to determine whether the chewing of SFG can be adopted as an intervention in other groups at increased risk of developing dental caries.

There are several limitations which should temper the conclusions that are drawn from this study. Studies not in the English language were excluded. This meant that six studies

relating specifically to the relationship between SFG use and caries were excluded – two of those studies were reporting findings for studies which did contribute English language manuscripts to this review. No attempt was made to explore the possibility of publication bias. Given the high degree of heterogeneity identified in the meta-analysis, a sensitivity analysis would have been useful to identify the variables that contributed to the heterogeneity.

No adverse events were reported, though this may in part be due to a lack of data collection – few studies reported active attempts to gather data on possible adverse events. Given concerns about the environmental impact of gum residue and potential objections such as school policies and perceived risks of choking (Glass 1983), this is certainly an area for future research and would benefit from qualitative studies exploring the perspectives of different socio-economic groups.

The search strategy was wide ranging and comprehensive, including review of the citations in all studies identified in the electronic searches. The grey and unpublished literature was not searched, but this is likely to have omitted studies with non-significant results. The quality of evidence was variable and it is clear that there is a need for better designed trials which include reporting of adverse events and measures of participant compliance with the intervention. Ten of the 14 studies were conducted in children, and there is a need for further studies in adult populations.

In conclusion there is evidence to support the use of sugar-free gum in the control of dental caries in children. Further research is required to assess the effect of SFGs on caries incidence in adults and also the specific value of using xylitol in this regard.

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The authors declare that there are no conflicts of interest in this publication.

Figure Legends

Figure 1: Search strategy for Ovid Medline, modified for other databases.

Figure 2: PRISMA flowchart of study identification, screening and inclusion.

Table 1: Summary of characteristics of included studies

Table 2: Risk of bias of included studies

Figure 3: Meta-analysis of any SFG and dental caries using the random-effects model by date of publication

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Wessel, SW, van der Mei, HC, Maitra, A, Dodds, MW, Busscher, HJ 2016. Potential benefits of chewing gum for the delivery of oral therapeutics and its possible role in oral healthcare. Expert opinion on drug delivery. 13(10):1421-1431.

Figure 1

1 Chewing Gum/
2 (chewing gum* or chewinggum*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3 1 or 2
4 (sugar free or sugar-free).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5 exp Sweetening Agents/
6 (sweetening agent* or artificial sweetener* or nutritive sweetener* or non-nutritive sweetner*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7 5 or 6
8 3 and 4
9 3 and 7
10 Oral Health/
11 8 and 10
12 9 and 10
13 exp Dental Caries/
14 (dental caries or dental decay or tooth decay or tooth caries).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15 13 or 14
16 8 and 15
17 9 and 15
18 exp Xerostomia/
19 (dry mouth or xerostomia or mouth dryness).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
20 18 or 19
21 8 and 20
22 9 and 20
23 exp Periodontal Diseases/
24 periodontal disease*.mp. or oral disease* or mucosal disease* [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
25 23 or 24
26 8 and 25
27 9 and 25
28 exp Smoking Cessation/
29 (smoking cessation or stop* smoking).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
30 28 or 29
31 8 and 30
32 9 and 30
33 exp Diet/
34 8 and 33
35 9 and 33

36	Sugars/
37	sugar*
38	36 or 37
39	38 not (4 or 5 or 6)
40	39 and 4
41	39 and 7
42	xylitol or polyol or maltitol or sorbitol or sucralose or stevia or aspartame

Figure 2: PRISMA flowchart of study identification, screening and inclusion.

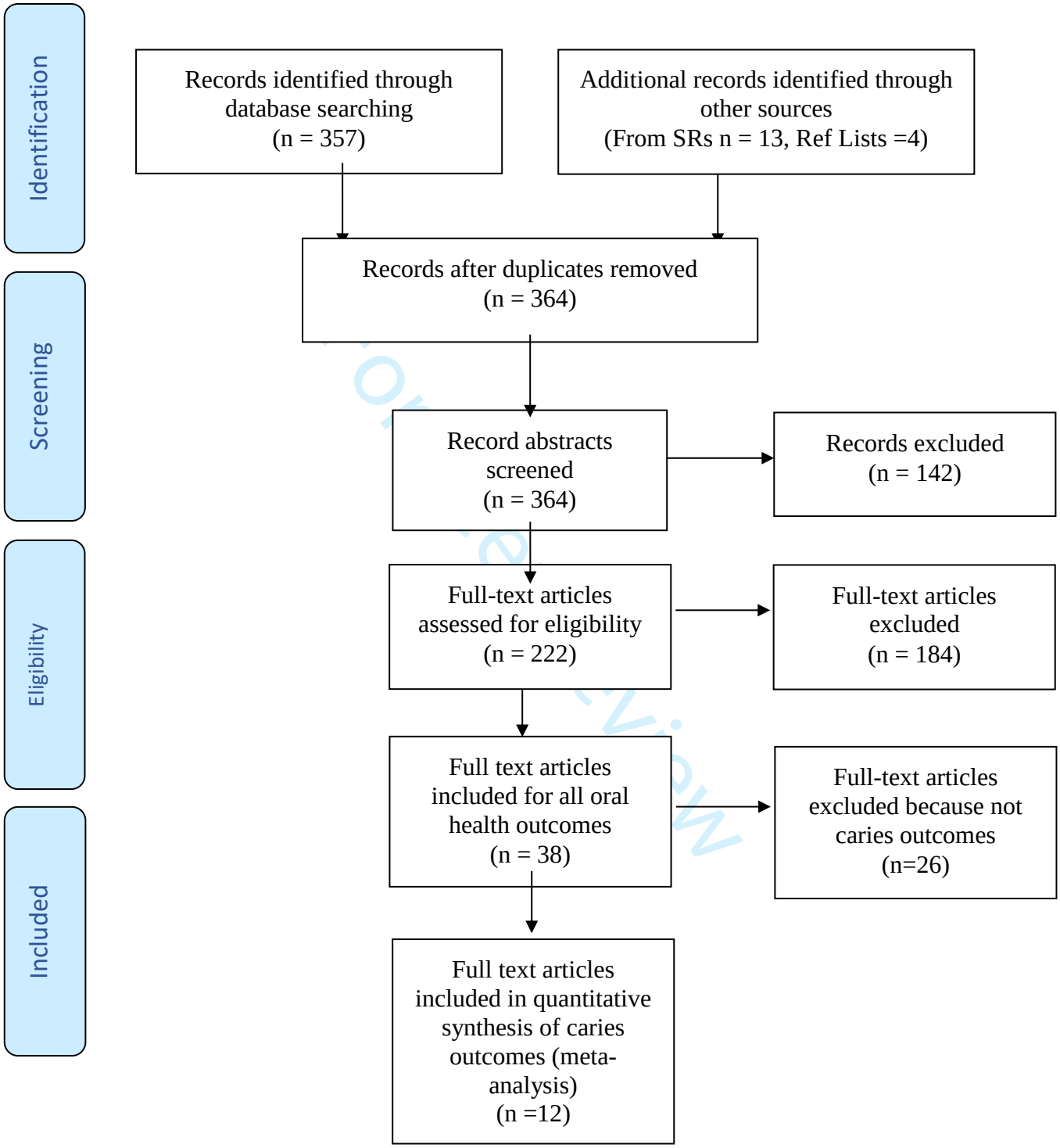

Table 1: Summary of characteristics of the included studies

Study citation	Intervention	Participant characteristics	Follow-up duration	Study design	Control: group	Intervention arms	Outcome measure	Mean caries increment / study arm
GLASS et al (1983)	Sorbitol gum over 2 years	N=540 children aged 7-11 years	2 years	RCT	No gum	Sorbitol gum Twice daily	Increment of dft	Control: 2.55 SFG: 2.53
KANDELMAN et al (1990)	Xylitol gum over 2 years	N=274 children aged 8-9 years	2 years	RCT	No gum	Gp1: 15% xylitol gum Gp2: 65% xylitol 3x / day	Increment of dmft	Control: 4.6 SFG: 1.47
BEISWANGER et al (1998)	Sorbitol gum over 2 years	N=1402 children aged 10-12 years	3 years	RCT	No gum	Gum 3x / day	Increment of dmft	Control: 8.58 SFG: 8.0
HUJOEL et al (1999); MAKINEN et al (1995a,b; 1996; 1998)	Xylitol gum Sorbitol gum Xylitol/Sorbitol mixture gum Over 1 yr; 5 yr follow up	N=298 children aged 6 years	5 years	pre-post trial	No gum	Xylitol gum Sorbitol gum Xylitol/Sorbitol mixed gum 3x / day	Increment of dmfs	Control: 4.0 SFG: 2.01
ALANEN et al (2000)	Xylitol gum over 3 years	N= 740 children aged 10 years	5 years	RCT	No gum	Xylitol gum 3x / day	Increment of dmfs	Control: 1.7 SFG: 1.95
MACHIULSKIENE et al (2001)	Xylitol gum Sorbitol gum Sorbitol / carbamide gum over 3 yrs	N=602 children aged 6-14 years	3 years	RCT	No gum	Xylitol gum Sorbitol/carbamide gum Sorbitol gum Control: gum	Increment of dmft	Control: 8.3 SFG: 8.1
KOVARI et al (2003)	Xylitol gum Over 1 year	N=1191 children aged 4-5 years	6 years	RCT	Tooth brushing	Xylitol gum 3x / day	Increment of dmfs	Control: 1.6 SFG: 1.2
SHOZE et al (2005)	Sorbitol gum over 2 years	N=547 children aged 7-11 years	2 years	RCT	No gum	Sorbitol gum 3x / day	Increment of dmfs	Control: 2.91 SFG: 1.95
SUZUKI et al (2011)	Xylitol gum over 3 months	N=161 children aged 3-4 years	9 months	RCT	Control: gum	Xylitol gum 3x / day	caries development	Control: 1.8 SFG: 1.6

AL-HABOUBI et al (2012)	Xylitol gum over 6 months	N=186 adults aged over 60 years	6 months	RCT	No gum	Xylitol gum Twice daily	Increment of DMFS	Control: 1.21 SFG: 1.51
ALAMOUDI et al (2012); HANNO et al (2011)	Xylitol gum over 3 mths	N=34 Mother-child dyads	18 months	RCT	Fluoride varnish	Xylitol gum 3x / day	Increment of DMFT	Control: 4.91 SFG: -0.2
TAO et al (2013)	Tea Polyphenol containing gum	N=157 children aged 8-9 years	2 years	RCT	No gum	Control: gum Tea polyphenol containing gum 3x / day	Increment of dmft	Control: 1.15 SFG: 0.6

Table 2: Risk of bias for the included studies.

Study	Study Design	Randomisation	Allocation concealment	Masking of participants	Masking of outcome assessors	Incomplete outcome reporting	Selective Reporting	Other bias
GLASS et al (1983)	RCT	Low risk	Unclear	High risk	Low risk	Unclear	Unclear	Unclear
RANDELMAN et al (1990)	RCT	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
BEISWANGER et al (1998)	RCT	Unclear	High risk	High risk	Low risk	Unclear	Unclear	Unclear
HUJOEL et al (1999); MAKINEN et al (1995a,b; 1996; 1998)	pre-post trial	High risk	High risk	High risk	Low risk	High risk	Low risk	Unclear
ALANEN et al (2000)	RCT	Low risk	Unclear	High risk	High risk	Unclear	Unclear	Unclear
MACHIULSKIENE et al (2001)	RCT	Low risk	Low risk	Low risk	Unclear	High risk	Unclear	Unclear
KOVARI et al (2003)	RCT	Low risk	Unclear	High risk	High risk	Unclear	Unclear	Unclear
AKOZE et al (2005)	RCT	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk
SEKI et al (2011)	RCT	Low risk	Low risk	Low risk	Unclear	High risk	Unclear	High risk
AL-HABOUBI et al (2012)	RCT	Low risk	Low risk	High risk	Low risk	Unclear	Unclear	Low risk
ALAMOUDI et al (2012); HANNO et al (2011)	RCT	Unclear	High risk	High risk	Unclear	Unclear	Unclear	Unclear
TAO et al (2013)	RCT	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear

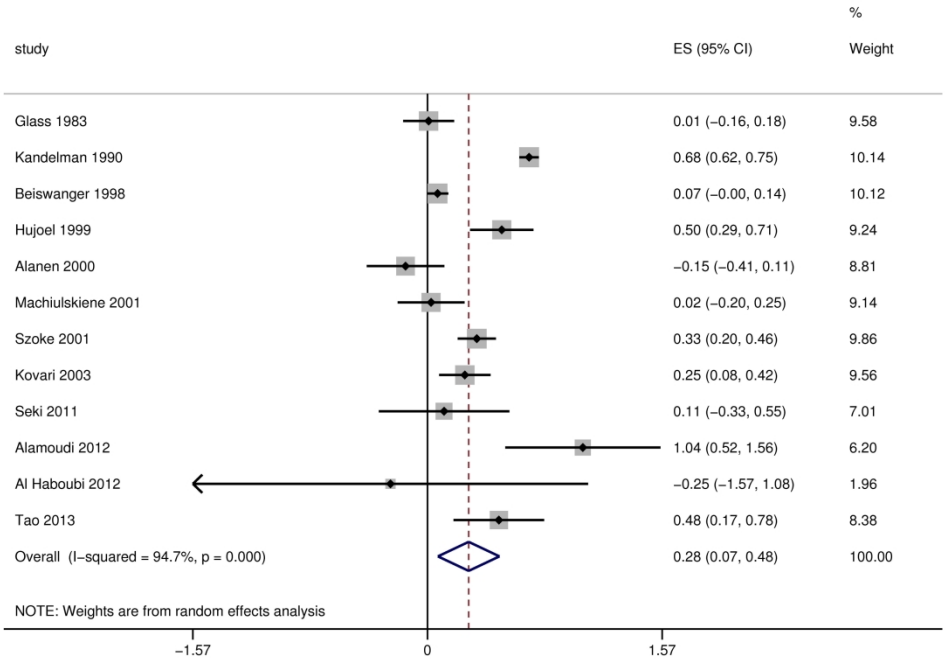

Figure 3: Meta-analysis of any SFG and dental caries using the random-effects model by date of publication

276x211mm (300 x 300 DPI)

Supplemental File: Excluded studies for Manuscript:

A systematic review and meta-analysis of the role of sugar-free chewing gum in dental caries
Manuscript CTR-19-RE-0074

EXCLUDED STUDIES – All outcomes (78)

Wash out shorter than 7 days

1. Mouton, C., et al. (1975). "Effect on plaque of a xylitol-containing chewing-gum: A clinical and biochemical study." Acta odontologica Scandinavica 33(1): 33-40.
2. Mouton, C., et al. (1975). "Effect on plaque of a xylitol-containing chewing-gum: A pilot study." Acta odontologica Scandinavica 33(1): 27-31.
3. Jensen, M. E. (1986). "Effects of chewing sorbitol gum and paraffin on human interproximal plaque pH." Caries Research 20(6): 503-509.
4. Davies, A. N. (2000). "A comparison of artificial saliva and chewing gum in the management of xerostomia in patients with advanced cancer." Palliative Medicine 14(3): 197-203.
5. Ainamo, J., et al. (1977). "Growth of plaque while chewing sucrose and sorbitol flavoured gum." Journal of clinical periodontology 4(3): 151-160.
6. Rios, D., et al. (2006). "Effect of salivary stimulation on erosion of human and bovine enamel subjected or not to subsequent abrasion: An in situ/ex vivo study." Caries Research 40(3): 218-223.
7. Etemadzadeh, H. (1991). "Plaque-growth inhibiting effect of chewing gum containing urea hydrogen peroxide." Journal of clinical periodontology 18(5): 337-340.
8. Imfeld, T., et al. (1995). "Effect of urea in sugar-free chewing gums on ph recovery in human dental plaque evaluated with 3 different methods." Caries Research 29(3): 172-180.
9. Antunes, D. P., et al. (2015). "Buffer capacity of saliva as a function of time after consumption of sugary, sugar-free and probiotic chewing gums." Pesquisa Brasileira em Odontopediatria e Clinica Integrada 15(1): 153-161.
10. Ballal, R. K., et al. (2016). "Effect of Chewing Bicarbonate-containing Sugar-free Gum on the Salivary pH: An in vivo Study." International journal of clinical pediatric dentistry 9(1): 35-38.
11. Hanham, A. and M. Addy (2001). "The effect of chewing sugar-free gum on plaque regrowth at smooth and occlusal surfaces." Journal of clinical periodontology 28(3): 255-257.
12. Olsson, H., et al. (1991). "The effect of a chewing gum on salivary secretion, oral mucosal friction, and the feeling of dry mouth in xerostomic patients." Acta odontologica Scandinavica 49(5): 273-279.
13. Pluss, E. M. (1978). "Effect on plaque growth of xylitol and sucrose-containing chewing gums." Journal of clinical periodontology 5(1): 35-40.
14. Murtomaa, H., et al. (1993). "The use of Xylitol chewing gum in oral health promotion for Finnish students." Health Promotion International 8(4): 271-274.
15. Anderson, L. A. and R. Orchardson (2003). "The effect of chewing bicarbonate-containing gum on salivary flow rate and pH in humans." Archives of Oral Biology 48(3): 201-204.
16. Lee, I. K. and C. F. Schachtele (1992). "Effect of gum chewing following food ingestion on the pH of interproximal dental plaque." Quintessence International 23(7): 455-459.

17. Manning, R. H., et al. (1992). "Effects of chewing gums sweetened with sorbitol or a sorbitol/xylitol mixture on the remineralisation of human enamel lesions in situ." Caries Research 26(2): 104-109.
18. Vantipalli, U. K., et al. (2017). "Effect of three commercially available chewing gums on salivary flow rate and pH in cariesactive and cariesfree children: An in vivo study." Journal of Indian Society of Pedodontics and Preventive Dentistry 35(3): 254-259.
19. Topitsoglou, V., et al. (1983). "Effect of chewing gums containing xylitol, sorbitol or a mixture of xylitol and sorbitol on plaque formation, pH changes and acid production in human dental plaque." Caries Research 17(4): 369-378.
20. Paice, E. M., et al. (2011). "The erosive effects of saliva following chewing gum on enamel and dentine: an ex vivo study." British Dental Journal 210(3): E3
21. Koparal, E., et al. (2000). "Effect of chewing gum on plaque acidogenicity." Journal of Clinical Pediatric Dentistry 24(2): 129-132.
22. Park, K. K., et al. (1990). "Effect of sorbitol gum chewing on plaque pH response after ingesting snacks containing predominantly sucrose or starch." American Journal of Dentistry 3(5): 185-191.
23. Silwood CJL, Grootveld MC, Lynch E: A multifactorial investigation of the ability of oral health care products (OHCPs) to alleviate oral malodour(2001) J Clin Periodontol ; 28: 634–641. C Munksgaard, 2001.
24. Sato S, Yoshinuma N, Ito K et al (1998) The inhibitory effect of funoran and eucalyptus extract-containing chewing gum on plaque formation. J Oral Sci 1998; 40: 115–117.
25. Lin, Y. T., et al. (2001). "Effects of fluoride chewing gum on stimulated salivary flow rate and fluoride content." Chang Gung Medical Journal 24(1): 44-49.
26. Fure, S., et al. (1998). "Effect of three months' frequent use of sugar-free chewing gum with and without urea on calculus formation." Journal of Dental Research 77(8): 1630-1637.
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28. Igarashi, K., et al. (1988). "Effect of chewing gum containing sodium bicarbonate on human interproximal plaque pH." Journal of Dental Research 67(3): 531-535.
29. Jensen, M. E. (1988). "Effects of chewing sorbitol gum on human salivary and interproximal plaque pH." Journal of Clinical Dentistry 1(1): 6-19.
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32. Rekola, M. (1988). "Acid production from xylitol products in vivo and in vitro." Proceedings of the Finnish Dental Society 84(1): 39-44.
33. Shannon, I. L. and W. J. Frome (1973). "Enhancement of salivary flow rate and buffering capacity." Journal of the Canadian Dental Association 39(3): 177-181.
34. Vratsanos, S. M. and I. D. Mandel (1981). "The effect of sucrose and hexitol--containing chewing gums on plaque acidogenesis in vivo." Pharmacology & Therapeutics in Dentistry 6(3-4): 87-91.
35. Park, K. K., et al. (1995). "Effect of chewing gums on plaque pH after a sucrose challenge." Journal of Dentistry for Children 62(3): 180-186.
36. Markovic, N., et al. (1988). "Sorbitol gum in xerostomics: the effects on dental plaque pH and salivary flow rates." Gerodontology 7(2): 71-75.

37. Abelson, D. C., et al. (1990). "The effect of chewing sorbitol-sweetened gum on salivary flow and cemental plaque pH in subjects with low salivary flow." Journal of Clinical Dentistry 2(1): 3-5.
38. Lif Holgerson, P., et al. (2006). "Xylitol concentration in saliva and dental plaque after use of various xylitol-containing products." Caries Research 40(5): 393-397.

Outcomes not relevant or the direct effect of SFG not primary focus of intervention

39. Frost, P. M., et al. (2002). "Patient preferences in a preliminary study comparing an intra-oral lubricating device with the usual dry mouth lubricating methods." British Dental Journal 193(7): 403-408. -
40. Machiulskiene, V., et al. (2002). "Determinants of dropout in a community intervention trial on the caries-preventive effect of chewing gums." Journal of Public Health Dentistry 62(1): 21-27.
41. Autio, J. T. and F. J. Courts (2001). "Acceptance of the xylitol chewing gum regimen by preschool children and teachers in a Head Start program: a pilot study." Pediatric Dentistry **23**(1): 71-74.
42. Dodds, M. W. J., et al. (1991). "The effect of increased mastication by daily gum-chewing on salivary-gland output and dental plaque acidogenicity." Journal of Dental Research 70(12): 1474-1478.
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45. Alamoudi, N. M., et al. (2012). "Impact of maternal xylitol consumption on mutans streptococci, plaque and caries levels in children." Journal of Clinical Pediatric Dentistry 37(2): 163-166.

Not SFG, not SFG alone or unclear if SFG

46. Ainamo, J. and H. Etemadzadeh (1987). "Prevention of plaque growth with chewing gum containing chlorhexidine acetate." Journal of clinical periodontology 14(9): 524-527.
47. Eghbali, A., et al. (2016). "Effect of Chewing Gum on Oral Mucositis in Children Undergoing Chemotherapy: A Randomized Controlled Study." Iranian Journal of Pediatric Hematology and Oncology 6(1): 9-14.
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54. Kandelman, D., et al. (1988). "Collaborative WHO xylitol field study in French Polynesia. I. Baseline prevalence and 32-month caries increment." Caries Research 22(1): 55-62.
55. Smith AJ, Moran J, Dangler LV, Leight RS, Addy M. 1996 The efficacy of an anti-gingivitis chewing gum. J Clin Periodontol; 23: 19–23.
56. Lin, Y. T. and R. E. Corpron (1991). "In vivo study of fluoride chewing gum for the remineralization of human root lesions." Changgeng Yi Xue Za Zhi 14(3): 174-185.
57. Topcuoglu, N., et al. (2015). "Antibacterial Effect of Kenger Gum on Mutans Streptococci and Its Cytotoxic Effect on the 3T3 Fibroblast Cell Line." Oral Health & Preventive Dentistry 13(2): 157-162.
58. Masalin, K. (1992). "Caries-risk-reducing effects of xylitol-containing chewing gum and tablets in confectionery workers in Finland." Community Dental Health 9(1): 3-10.

Not trials/experimental studies (reviews/commentaries)

59. Tsao, C. E. and M. V. Morgan (2005). "Does chewing sucrose-free chewing gum after meals reduce the development of carious lesions?" Medical Journal of Australia 182(2): 85-86.
60. Gray, D. L. (2012). "The wichita xylitol project-a viable in-school alternative to fluoride for caries prevention." Fluoride 45(4): 323-328.

Not trials/experimental studies and participants not analysed in their original allocated groups

61. Soderling, E., et al. (1991). "Long-term xylitol consumption and mutans streptococci in plaque and saliva." Caries Research 25(2): 153-157.
62. Isogangas, P., et al. (1993). "Long-term effect of xylitol chewing gum in the prevention of dental caries: a follow-up 5 years after termination of a prevention program." Caries Research 27(6): 495-498.
63. Isokangas, P., et al. (1991). "Dental caries and mutans streptococci in the proximal areas of molars affected by the habitual use of xylitol chewing gum." Caries Research 25(6): 444-448.

Foreign language papers

64. Buhmann, A. G., et al. (1991). "Tooth protecting chewing gum tablets for lessening caries risk." Oral-prophylaxe / Herausgeber, Verein fur Zahnhygiene e.V 13(4): 142-147.
65. Hase, J. C., et al. (1992). "An individual training-program for speeding up prolonged oral sugar clearance in hospitalized elderly patients - a pilot-study." Swedish dental journal 16(6): 239-245.
66. Li, X. J., et al. (2010). "[Comparative effects of the maltitol chewing gums on reducing plaque]." Hua Xi Kou Qiang Yi Xue Za Zhi 28(5): 502-504.
67. Porciani, P. F., et al. (1992). "[The action on bacterial plaque of the mastication of a sorbitol chewing gum]." Minerva Stomatologica 41(10): 445-449.
68. Rekola, M. (1989). "[Effect of Xylitol chewing gum on total saliva and dental plaque in caries-active persons]." Oral-Prophylaxe 11(3): 95-100.
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70. Rumiantsev, V. A., et al. (2011). "[Sugar of substitute stevioside in chewing gum: comparative double blind controllable study]." Stomatologiia 90(1): 18-21.
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73. Makinen, K. K. and A. Scheinin (1975). "[Sugar studies in Abo. Report of clinical long-range studies]." Tandlakartidningen 67(1): 8-20. [SWEDEN]
74. Kertesz, P., et al. (1988). "[3 years' results of the WHO xylitol caries-preventing program in Hungarian children's homes. VI. Changes in the carbohydrate-protein ratio in dental plaque]." Fogorvosi Szemle 81(2): 33-37. [HUNGARIAN]
75. Tsapok, P. I., et al. (2012). "[Sugar substitute products impact on oral fluid biochemical properties]." Stomatologiia 91(2): 23-25.
76. Szoke, J., et al. (2002). "[Effect of chewing sugar-free gum on dental caries]." Fogorvosi Szemle 95(1): 21-25.
77. Scheinin, A. and K. K. Makinen (1977). "Effect of consumption of certain sugars on the incidence of dental caries in man." Czasopismo Stomatologisczne 30(6): 481-489.
78. Shu, C., et al. (2007). "Effect of two kinds of chewing gums on dental plaque pH." Shanghai kou qiang yi xue = Shanghai journal of stomatology 16(2): 172-175.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 & Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 & Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 & Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9 & Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9, 10 Figures 3 and 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 3 and 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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